

substantial, if not complete, deletion of the long arm at Yq11.1. A negative result with probe pJG1.0 also confirmed that the long arm of the Y was deleted. Munke *et al*<sup>9</sup> have suggested that azoospermia in phenotypically normal males with Yq deletions is more likely to be the result of an inability of the X and Y chromosomes to pair normally during meiosis than an absence of a fertility gene located somewhere on the Y long arm.

The short stature of our patient would imply that the gene for growth promoting factors is localised somewhere on the long arm of Y, distal to q11.1, although his short stature may be entirely because of the XO cell line. Furthermore, patients with ring Y and normal height have been reported,<sup>9</sup> although the actual extent of the deletion in ring Y chromosomes is difficult to estimate.

Buhler<sup>1</sup> has suggested that the height regulating genes may be located on both arms of the Y. Short stature has also been reported in deletions involving the proximal Yq11 region<sup>9</sup> and our patient's deleted Y chromosome appears to confirm this observation and to define this locus even more accurately, that is, at or above Yq11.1. Defining the extent of a deletion in small chromosomes is difficult but the application of recombinant DNA technology has proved useful in establishing that the tiny chromosome of our patient is actually a Y, is not a ring, is substantially deleted in the long arm (apparently at q11.1), and presents as a low grade mosaic.

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## Toluene embryopathy: two new cases

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**SUMMARY** Toluene embryopathy is characterised by microcephaly, central nervous system

dysfunction, attentional deficits and hyperactivity, developmental delay with greater language deficits, minor craniofacial and limb anomalies, and variable growth deficiency.

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Previously, three affected children, born to women who inhaled toluene regularly throughout pregnancy, have been reported. Two more cases are described emphasising the importance of toluene as a potential human teratogen.

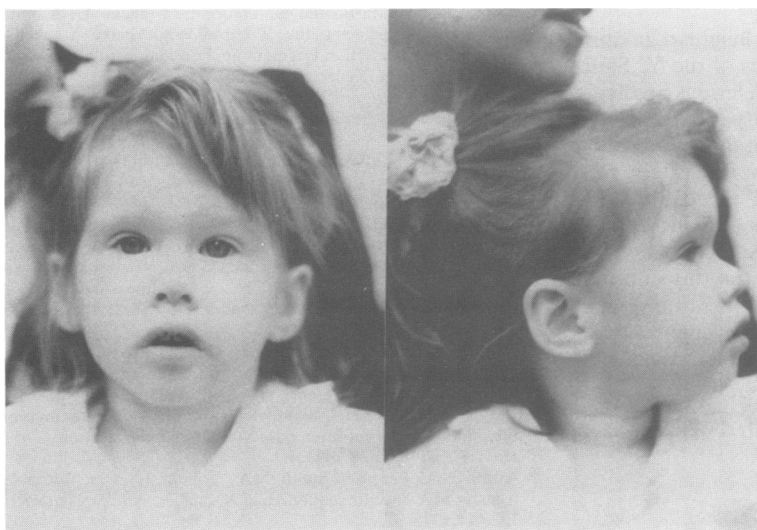
Toluene is an aromatic hydrocarbon commonly used as a solvent or thinner in a number of industrial products.<sup>1</sup> Exposure in humans primarily occurs in an occupational setting. However, toluene is also abused recreationally through inhalation.

Evidence for teratogenicity as a result of occupa-

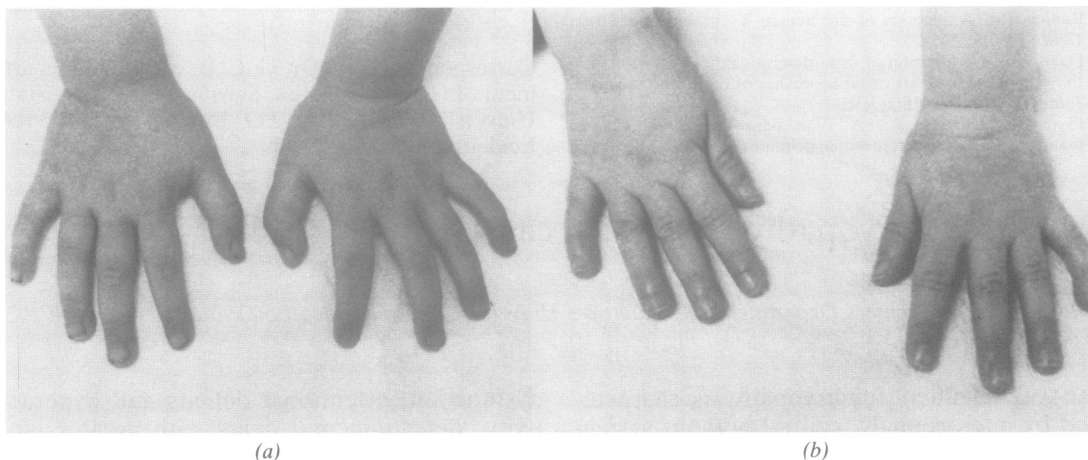
tional exposure to toluene prenatally has been inconclusive. In 1985, three children with microcephaly, central nervous system dysfunction, minor craniofacial and limb anomalies, and variable growth deficiency, born to women who chronically inhaled toluene throughout pregnancy, were reported.<sup>2</sup> Two more cases of toluene embryopathy are described, further emphasising the potential for teratogenicity from chronic in utero exposure to this solvent.

### Case reports

Patient 1 (figs 1 and 2a) is a white female who was



**FIG 1** Patient 1 at three years two months. Note the short palpebral fissures, deep set eyes, small midface, flat nasal bridge, small nose, low set ears, deficient philtrum, and micrognathia.



**FIG 2** Hands of patient 1 (a) and patient 2 (b). Note the blunt fingertips in both and apparently small fingernails in patient 1.

evaluated because of developmental delay. She was born at 35 weeks' gestation to a 22 year old G2P1 woman who had a seven year history of regular inhalation of pure toluene paint reducer and spray paint. In adolescence, other substance abuse was reported. During pregnancy, she frequently inhaled toluene paint reducer, but no alcohol or other substances were used. The father was 29 years old and there was no consanguinity.

At birth, her weight was 2360 g (50th centile), length 46 cm (50th centile), and occipitofrontal circumference 30.5 cm (25th centile). There were no neonatal complications.

Developmental delay was recognised in infancy. Diagnostic studies to determine its aetiology included normal TORCH titres, computerised tomography of the head, fragile X chromosome analysis, urine amino acid screen, and thyroid function.

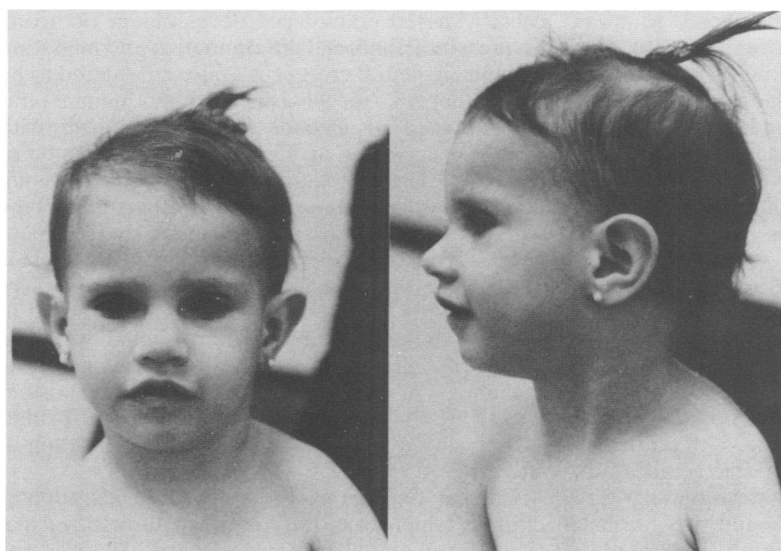


FIG 3 Patient 2 at 20 months. Note the short palpebral fissures, deep set eyes, small midface, slightly flattened nasal bridge, small nose, prominent ears, and micrognathia.

TABLE Clinical features in toluene embryopathy.

	Patient 1 (3 y 2 mth)	Patient 2 (20 mth)	Hersh et al <sup>2</sup>
Microcephaly	—	+	3/3
Abnormal scalp hair pattern	—	—	2/3
Narrow bifrontal diameter	+	+	3/3
Strabismus	—	—	1/3
Short palpebral fissures	+	+	3/3
Deep set eyes	+	+	3/3
Epicanthic folds	—	—	1/3
Small midface	+	+	3/3
Low set or prominent ears	+	+	3/3
Flat nasal bridge	+	+	2/3
Small nose	+	+	2/3
Deficient philtrum	+	—	1/2
Thin upper lip	—	—	1/3
Micrognathia	+	+	3/3
Blunt fingertips	+	+	3/3
Small fingernails	+	—	3/3
Abnormal palmar creases	—	+	2/3
Cryptorchidism	—	—	1/2
Abnormal muscle tone	Hypotonia	Hypertonia	Hypotonia 3/3
Hyperreflexia	—	—	3/3
Attentional deficits and/or hyperactivity	—	+	3/3
Renal anomaly	—	—	2/3

Psychological testing at three years two months indicated a mental age of three years two months with an IQ of 86 on the Stanford-Binet Intelligence Scale, Form LM. Receptive language abilities were comparable to her mental age and she had a mild expressive language impairment and a speech articulation disorder. There were no attentional problems.

At three years two months her length was 91 cm (10th centile), weight 13.3 kg (10th centile), and OFC 47 cm (5th centile). Physical findings are listed in the table. Renal ultrasound was normal.

Patient 2 (figs 2b and 3) is a white female who was evaluated because of poor weight gain. She was born at term to a 28 year old primigravida who had at least a 10 year history of regular inhalation abuse of toluene that resulted in mild ataxia, tremor, and slurred speech. During pregnancy, toluene paint reducer was sniffed almost daily. She occasionally consumed alcohol, but did not have any other substance abuse. The father was 29 years old and there was no consanguinity.

At birth, her weight was 2550 g (slightly <10th centile) and length 48 cm (slightly >25th centile). Other than expressive language delay, early developmental milestones appeared normal. She had a short attention span.

At 20 months she had a length of 80.5 cm (25th centile), weight 8.2 kg (<5th centile, 50th centile for eight months), and OFC 43.2 cm (<5th centile, 50th centile for seven months). Physical findings are listed in the table. Renal ultrasound was normal. Psychological testing at 21 months indicated a mental age of 17½ months and a motor age of 18 months on the Bayley Scales of Infant Development. Language impairment was noted relative to her mental age.

## Discussion

With two additional cases, we have now identified five children with features of toluene embryopathy.<sup>2</sup> In all instances, there was chronic maternal inhalation abuse before and throughout pregnancy, without evidence of excessive use of other substances. Based on the clinical features of affected subjects, the most frequent manifestations of this recognisable pattern of malformation include microcephaly, central nervous system dysfunction, attentional deficits or hyperactivity or both, developmental delay with greater language impairment, and growth retardation. Common phenotypic abnormalities are a small midface, narrow bifrontal diameter, short palpebral fissures with deep set eyes, low set ears, flat nasal bridge with a small nose, micrognathia,

and blunt fingertips. Urinary tract anomalies, discovered in two of the three original patients, including a lesion in a child who also had a single umbilical artery,<sup>2</sup> were not present in either of our cases, and no other structural abnormalities were present.

Although the pathogenesis of toluene embryopathy has not been determined, we have previously suggested that alterations in brain development and facial morphogenesis may result from a deficiency in the neural plate, leading to abnormal proliferation and migration of neural crest cells.<sup>2</sup> Altered craniofacial development occurring as a result of abnormal differentiation and migration of cephalic neural crest cells is also considered to be the pathogenic mechanism of other human teratogens, such as alcohol and retinoic acid with exposure occurring at a critical period of embryogenesis.<sup>3-4</sup> These similarities emphasise the potential existence of a non-specific teratogenic phenotype with abnormal growth, development, and morphogenesis as a consequence of this disturbance. It is anticipated that variability in clinical features of patients with toluene embryopathy and absence of manifestations in others after similar prenatal exposure will result from a number of factors including the duration and intensity of exposure, nature of the preparation, interaction with other agents, and especially the genetic predisposition of the exposed fetus.<sup>5</sup>

Clinical findings in these five patients support chronic toluene exposure in utero through inhalation as a potential human teratogen. There is one other recent report of an infant described as having similar craniofacial anomalies, microcephaly, and stubby fingertips whose mother abused spray paint during pregnancy.<sup>6</sup> The prevalence of toluene embryopathy among solvent abusers and the amount of prenatal exposure necessary to result in adverse fetal effects is yet to be determined. In addition, the impact of polydrug use on the phenotype will need to be assessed, although presumably this did not represent a confounding issue in our patients, since substance abuse was primarily limited to toluene inhalation. It is anticipated that continued evaluation of physical characteristics, growth, and development of infants exposed to toluene in utero should help to answer these questions.

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## Synchrony of oculocutaneous albinism, the Prader-Willi syndrome, and a normal karyotype

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**SUMMARY** A Chinese girl with oculocutaneous albinism has the Prader-Willi syndrome and a normal karyotype. This association emphasises the importance of further molecular study of the 15(q12) region of the genome in the search for the locus of an albinism gene.

Using current cytogenetic techniques, about 50% of subjects with the Prader-Willi syndrome are shown to have a normal karyotype, while the remainder display an interstitial deletion of 15(q12).<sup>1</sup> There are no distinguishing phenotypic features between these two groups.<sup>2</sup>

Hypopigmentation has been recognised as a component of Prader-Willi syndrome<sup>3,4</sup> and a black infant with albinism, the Prader-Willi phenotype, and a deletion involving band 15(q11.2) has recently been documented.<sup>5</sup>

In this report we present the clinical features of a girl with oculocutaneous albinism and the Prader-Willi syndrome who has a normal karyotype. This observation prompts further speculation regarding the potential presence of a gene for albinism at the locus 15(q12).

### Case report

The proband, a girl born in 1981 (figure), was the first child of young, non-consanguineous, Chinese parents living on the Indian Ocean island of Mauritius. Both parents and two younger sibs were in good health and there was no history of genetic disease in the extended family. The pregnancy was uncomplicated and delivery occurred normally at term. During the neonatal period the child was hypotonic and required tube feeding for the first 10

weeks of life. By six months of age oculocutaneous albinism was diagnosed clinically. At this time her psychomotor development was delayed by three months.

At the age of three years, she walked and understood simple commands although she was unable to speak. Her behaviour was characterised by temper tantrums, she had a voracious appetite, and her weight was on the 97th centile.

In 1987 at the age of six years, physical examination showed the following features. Her height was 115 cm (50th centile) and she weighed 24 kg (90th centile). Her skin, hair, and irides lacked pigment and she had nystagmus, photophobia, a right convergent squint, severe myopia, and pale retinæ. She had truncal obesity with tapering of the limbs and small hands and feet. Her IQ was estimated to be in the 30 to 50 range, vocabulary was limited to a few single words, and gross motor function was delayed. Hearing was normal, there was no evidence of any neuromuscular deficit or systemic disease, and there were no additional dysmorphic features. Her genitalia were normal for a prepubertal female.

Cytogenetic studies were performed on peripheral blood lymphocytes. Analysis of G banded chromosomes, containing up to 850 bands per haploid set, showed a normal karyotype without evidence of a deletion in the long arm of chromosome 15. No facilities were available for measurement of hair bulb tyrosinase activity.